

Original Article



Real Clinical Practice Data of Monthly Dupilumab Therapy in Adult Patients With Moderate-to-Severe Atopic Dermatitis: Clinical Efficacy and Predictive Markers for a Favorable Clinical Response

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ABSTRACT

Purpose: Dupilumab is recommended to be administered biweekly to treat adult patients with moderate-to-severe atopic dermatitis (AD). Real clinical practice data on the clinical efficacy of monthly dupilumab therapy are limited. We analyzed real clinical practice data on the clinical efficacy of monthly dupilumab therapy and predictive markers for favorable clinical responses to the therapy.

Methods: Medical records of 57 adult patients with moderate-to-severe AD who received dupilumab therapy every 4 weeks for 16 weeks were analyzed retrospectively. Eczema Area and Severity Index (EASI) were recorded at baseline and week 16. Clinical responses to monthly dupilumab therapy were defined as the proportion of patients with decreased EASI scores of at least 50% or 75% from baseline at week 16 (EASI-50 or EASI-75). Blood eosinophil counts and serum lactate dehydrogenase (LDH) levels were measured at baseline and week 16.

Results: Monthly dupilumab therapy showed EASI-50 and EASI-75 clinical responses in 48 (84.2%) and 27 (47.4%) of 57 patients at week 16, respectively. The percentage decrease in EASI scores from baseline at week 16 was significantly inversely correlated with baseline blood eosinophil count (correlation coefficient [r] = -0.405, P = 0.002) and baseline serum LDH level (r = -0.466, P < 0.001). The EASI-75 response rate was higher in patients with low (< 500/ μ L, 73.3%) than in those with high (\geq 500/ μ L, 37.5%) baseline blood eosinophil counts (P = 0.032), and was higher in patients with low (< 400 U/L, 55.6%) than those with high (\geq 400 U/L, 10.0%) baseline serum LDH levels (P = 0.013).

Conclusions: Monthly dupilumab therapy was clinically effective in adult patients with moderate-to-severe AD in real clinical practice. Baseline blood eosinophil count and serum LDH level could be predictive markers for clinical response to dupilumab therapy.

Keywords: Atopic dermatitis; dupilumab; clinical efficacy; eosinophil; IL-4; marker

Disclosure

There are no financial or other issues that might lead to conflict of interest.

INTRODUCTION

Atopic dermatitis (AD) is a common allergic disorder characterized by chronic inflammation, itching, dryness, and exudation of the skin. AD is commonly associated with a personal or family history of allergic disorders.^{1,2} AD appears to be initiated and maintained by the complex interactions among genetic predisposition, environmental triggers, immune dysfunction, hypersensitivity reactions, and skin barrier defects.^{3,4}

The standard medical treatment for AD is topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs), which relieve symptoms and skin inflammation. However, their clinical efficacy is transient, limited, and often disappointing to many patients with AD and physicians.⁵ Although a significant number of patients with severe AD show improvements following systemic treatment with cyclosporine, mycophenolate, methotrexate, or azathioprine, toxicity is possible with long-term treatment.^{1,6,7}

Dupilumab is a monoclonal antibody to interleukin (IL)-4 receptor alpha, which showed significant clinical benefits in patients with moderate-to-severe AD.⁸⁻¹⁰ Recently, real clinical practice data have shown clinical outcomes similar to those of randomized controlled trials (RCTs).¹¹⁻¹⁵ Most of the data on the clinical efficacy of dupilumab therapy derived from RCTs and real-world studies were based on biweekly therapy. However, the high cost of biweekly dupilumab therapy could be a financial burden to patients.¹⁶ Moreover, the clinical efficacies of monthly and biweekly dupilumab therapy for AD were not significantly different in RCTs without concomitant medications.¹⁷⁻¹⁸ To date, real clinical practice data on the clinical efficacy of monthly dupilumab therapy are limited.

We analyzed the real clinical practice data of patients with moderate-to-severe AD who were treated with monthly dupilumab therapy to investigate the clinical efficacy of this regimen and identify potential predictive markers for a favorable clinical response.

MATERIALS AND METHODS**Study design**

This study was a retrospective analysis of the electronic medical records of adult patients with moderate-to-severe AD who received monthly dupilumab therapy at a single academic center from August 2018 to August 2019. The institutional review board approved this study (IRB No. AJIRB-MED-MDB-19-370).

Study patients

A total of 117 adult patients (age ≥ 18 years) with moderate-to-severe AD received dupilumab therapy more than once at our clinic during the study period. We analyzed the clinical data of 57 patients (44 men and 13 women) who had received dupilumab therapy (300 mg subcutaneous for maintenance injection) every 4 weeks for 16 weeks. The baseline of this study was defined as the timing of initiation of monthly dupilumab therapy.

Demographic and clinical characteristics were collected at baseline: age, sex, onset age and duration of AD, body mass index (BMI), comorbid allergic diseases, the severity scores of AD including Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), and Investigator's Global Assessment (IGA, **Table 1**).¹⁹⁻²¹ Dupilumab was administered at an initial

Table 1. Baseline clinical and laboratory characteristics of 57 adult patients with moderate-to-severe atopic dermatitis who received monthly dupilumab therapy

Variables	Values
Age (yr)	30.1 ± 8.7
Sex	
Male	44 (77.2)
Female	13 (22.8)
Onset age of AD (yr)	8.0 ± 10.5
Duration of AD (yr)	22.1 ± 8.9
BMI (kg/m ²)	22.0 ± 2.9
Comorbid allergic disease	
Asthma	2 (3.5)
Allergic rhinitis	13 (22.8)
Allergic conjunctivitis	4 (7.0)
Urticaria	5 (8.8)
Severity scores of AD	
EASI score	27.8 ± 11.1
Moderate AD (7 ≤ EASI score < 21)	15 (26.3)
Severe AD (EASI score ≥ 21)	42 (73.7)
SCORAD score	66.7 ± 12.9
IGA score	
3 (moderate)	15 (26.3)
4 (severe)	42 (73.7)
Total IgE (kU/L)	3,116.3 ± 1,844.2
Blood eosinophil count (/μL)	1,000.0 ± 753.3
Serum LDH (U/L)	327.7 ± 110.5
Concomitant treatment	
Oral methotrexate	40 (70.2)
Topical calcineurin inhibitor	20 (35.1)
Topical corticosteroids	16 (28.1)
Allergen immunotherapy	12 (21.1)
Oral corticosteroids	4 (7.0)
Oral cyclosporine	4 (7.0)

Data are presented as mean ± standard deviation or number (%).

AD, atopic dermatitis; BMI, body mass index; EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; IGA, Investigator's Global Assessment; LDH, lactate dehydrogenase.

loading dose of 600 mg (loading dose) or 300 mg at baseline. The initial dose of dupilumab was not decided by the physicians but by the patients (mainly based on their economic capacity).

Assessment of clinical efficacy and safety

Clinical severity scores were recorded every 4 weeks by the physicians before administering dupilumab. Clinical responses were defined as the proportion of patients who achieved a decrease of at least 50% or 75% in the EASI score from baseline at week 16 (EASI-50 or EASI-75, respectively). We analyzed the clinical characteristics of the patients who showed a favorable clinical response to monthly dupilumab therapy, which was defined as the achievement of EASI-75 response at week 16 (EASI-75 responder/non-responder). The percentage decrease in the SCORAD score from baseline at week 16 and the proportion of patients who showed a decrease ≥ 2 in the IGA score from baseline at week 16 were also analyzed.

Concomitant treatments such as TCS, TCI, oral corticosteroids, oral cyclosporine, oral methotrexate, and allergen immunotherapy were continued according to the patient's clinical condition. Adverse events during monthly dupilumab therapy were assessed at every visit and recorded. The types and onset of adverse events were recorded in detail.

Assessment of laboratory parameters

The following baseline laboratory parameters were measured at the central laboratory of our hospital: blood eosinophil count, serum lactate dehydrogenase (LDH) level, serum levels of total immunoglobulin E (IgE) and specific IgE to house dust mites (HDM, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), molds (*Candida albicans*, *Pityrosporum orbiculare*, and *Trichophyton rubrum*), and animal (cat and dog) dander at baseline. Blood eosinophil counts and serum LDH levels were measured at week 16, and serum levels of total IgE and HDM-specific IgE were measured at week 52.

Blood eosinophil counts and serum LDH levels were measured using an automated hematology analyzer (Coulter Counter STKS; Beckman Coulter, Fullerton, CA, USA) and a Cobas c702 analyzer (Roche Diagnostics, Basel, Switzerland), respectively. Serum levels of total IgE and specific IgE were measured using the ImmunoCAP[®] assay (Thermo Fisher Scientific, Waltham, MA, USA) and ranged 2–5,000 kU/L and 0.35–100 kU/L, respectively. Measured serum levels of total IgE or specific IgE over the upper limits were set as 5,000 kU/L or 100 kU/L for the statistical analyses.

Baseline allergen-specific IgE levels determined the number of sensitized allergen groups (regarded as positive sensitization when the serum specific IgE level ≥ 0.35 kU/L); HDM, molds, and animal dander were classified into different groups, which ranged 0–3. For example, if a patient was sensitive to HDM and dog dander, the number of sensitized allergen groups was 2.

Statistical analysis

Data on baseline clinical characteristics are presented as mean \pm standard deviation (SD) or number (%). The Wilcoxon signed-rank test was used to determine the statistical significance of changes in the clinical severity score and laboratory parameters from baseline at week 16. The Mann-Whitney U test or χ^2 test (Fisher's exact test was used when more than 20% of cells in the contingency table have expected frequencies less than 5) was used to compare continuous or categorical variables between EASI-75 responders and non-responders. Correlations between 2 parameters were evaluated using Spearman's rank correlation analysis. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics ver. 25 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics of study subjects

Baseline demographic and clinical characteristics of the 57 patients with moderate-to-severe AD are summarized in **Table 1**. The mean (\pm SD) age of the patients was 30.1 ± 8.7 years, and 44 (77.2%) and 13 (22.8%) were male and female, respectively. AD started at the age of 8.0 ± 10.5 years and persisted for 22.1 ± 8.9 years. Baseline EASI and SCORAD scores were 27.8 ± 11.1 and 66.7 ± 12.9 , respectively, and 42 (73.7%) of the 57 patients were classified as having severe AD with an EASI score ≥ 21 .²² Furthermore, 15 (26.3%) and 42 (73.7%) patients had IGA scores of 3 and 4, respectively (**Table 1**).

Clinical efficacy

Changes in clinical severity scores during the monthly dupilumab therapy are described in **Table 2**. The EASI score significantly decreased from baseline (27.8 ± 11.1) to week 16 (8.7 ± 7.8 ; $P < 0.001$). The mean percentage change in the EASI score from baseline at week 16 was $-68.4\% \pm 25.9\%$. EASI-50, EASI-75, and EASI-90 responses at week 16 were observed in 48 (84.2%), 27 (47.4%), and 9 (15.8%) patients, respectively (**Table 2** and **Fig. 1**). When clinical response rate was adjusted by including patients with self-discontinuation due to insufficient clinical response or exacerbation ($n = 13$) as non-responders, the EASI-50 and EASI-75 response rates were 68.6% (48/70 patients) and 38.5% (27/70 patients), respectively. The worst-case EASI-50 and EASI-75 response rates, which were calculated including 13 patients mentioned above plus 30 patients with the loss to follow-up or no response to a telephone survey as non-responders, were 48.0% (48/100 patients) and 27.0% (27/100 patients), respectively.²³

The SCORAD score significantly decreased from baseline (66.7 ± 12.9) to week 16 (33.0 ± 14.1). The mean percentage change in SCORAD score from baseline at week 16 was $-51.1\% \pm 21.1\%$. A decrease in IGA score ≥ 2 points from baseline at week 16 was observed in 18 (41.9%) of 43 patients (**Table 2**).

Clinical and laboratory markers for predicting a favorable clinical response

The percentage decrease in the EASI score from baseline at week 16 was significantly inversely correlated with baseline blood eosinophil count ($n = 55$, $r = -0.405$, $P = 0.002$) and baseline serum LDH levels ($n = 55$, $r = -0.466$, $P < 0.001$; **Fig. 2**).

Table 2. Changes in clinical severity scores of atopic dermatitis during monthly dupilumab therapy

Outcomes	Baseline	Week 4	Week 8	Week 12	Week 16
EASI score	27.8 ± 11.1 ($n = 57$)	$16.4 \pm 7.8^*$ ($n = 54$)	$12.5 \pm 7.6^*$ ($n = 46$)	$10.5 \pm 7.9^*$ ($n = 47$)	$8.7 \pm 7.8^*$ ($n = 57$)
Change in EASI score		-35.9 ± 26.0	-57.4 ± 20.3	-63.2 ± 22.6	-68.4 ± 25.9
EASI-50		11 (20.4)	30 (65.2)	33 (70.2)	48 (84.2%)
EASI-75		2 (3.7)	11 (23.9)	15 (31.9)	27 (47.4%)
EASI-90		1 (1.9)	2 (4.3)	6 (12.8)	9 (15.8%)
SCORAD score	66.7 ± 12.9 ($n = 56$)	$46.6 \pm 14.8^*$ ($n = 54$)	$39.6 \pm 14.1^*$ ($n = 46$)	$36.7 \pm 14.8^*$ ($n = 49$)	$33.0 \pm 14.1^*$ ($n = 42$)
Change in SCORAD score (%)		-29.6 ± 18.9	-42.3 ± 16.7	-45.4 ± 20.5	-51.1 ± 21.1
IGA score ≥ 3	57/57 (100.0)	47/54 (82.5)	30/46 (65.2)	28/48 (58.3)	21/43 (48.8)
Decrease in IGA score ≥ 2 from baseline		3/54 (5.6%)	7/46 (15.2%)	16/49 (32.6%)	18/43 (41.9%)

Data are presented as mean \pm standard deviation or n/n_{total} (%).

EASI, Eczema Area and Severity Index; SD, standard deviation; EASI-50, a decrease of at least 50% in the EASI score from baseline; EASI-75, a decrease of at least 75% in the EASI score from baseline; EASI-90, a decrease of at least 90% in the EASI score from baseline; SCORAD, Scoring Atopic Dermatitis; IGA, Investigator's Global Assessment.

* $P < 0.001$ compared to baseline using Wilcoxon signed-rank test.

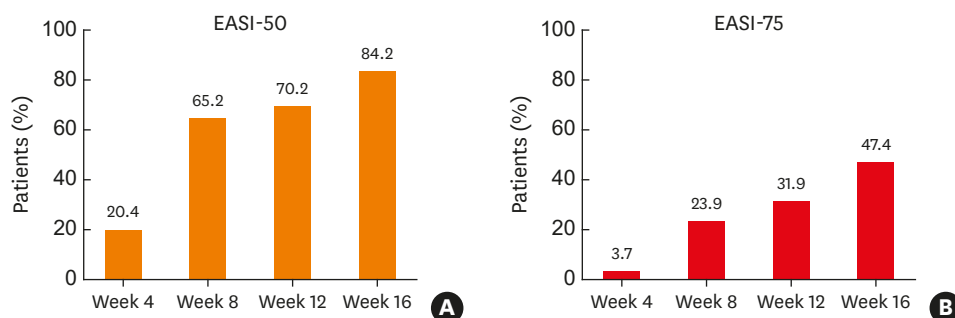


Fig. 1. Proportions of patients achieving favorable clinical responses: EASI-50 (A) and EASI-75 (B) at week 4, 8, 12, and 16 in 57 patients with moderate-to-severe AD who received monthly dupilumab therapy.

EASI, Eczema Area and Severity Index; EASI-50, a decrease of at least 50% in the EASI score from baseline; EASI-75, a decrease of at least 75% in the EASI score from baseline; AD, atopic dermatitis.

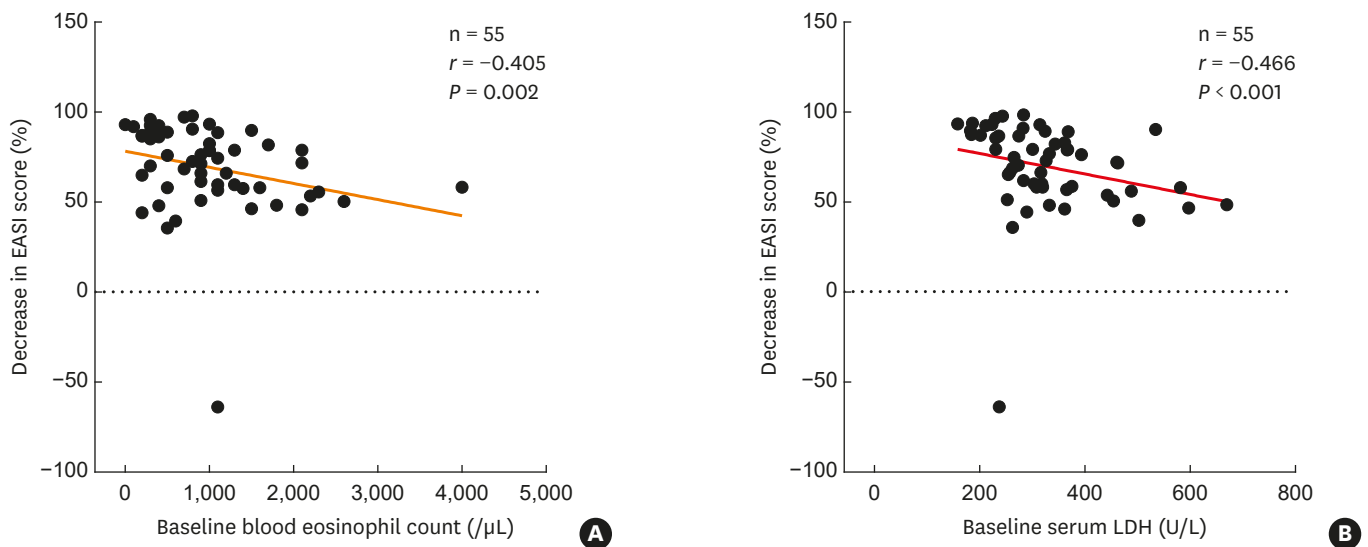


Fig. 2. Correlations of baseline blood eosinophil counts (A) and serum LDH levels (B) with percentage decreases in EASI scores from baseline at week 16 in 55 patients with AD who received monthly dupilumab therapy. *P* values were calculated using Spearman correlation analysis. LDH, lactate dehydrogenase; EASI, Eczema Area and Severity Index; AD, atopic dermatitis.

There was no significant difference in baseline clinical characteristics (age, the proportion of male patients, onset age and duration of AD, BMI, the initial dose of dupilumab, and baseline EASI score) between EASI-75 responders and non-responders to monthly dupilumab therapy for 16 weeks (**Table 3**). The baseline total IgE level was not significantly different between EASI-75 responders and non-responders ($2,881.6 \pm 1,868.3$ kU/L vs. $3,336.9 \pm 1,825.5$ kU/L; $P = 0.278$). The baseline blood eosinophil count was significantly lower in EASI-75 responders than in EASI-75 non-responders ($719.2 \pm 526.9/\mu\text{L}$ vs. $1,251.7 \pm 841.2/\mu\text{L}$; $P = 0.008$). The EASI-75 response rate at week 16 was significantly higher in patients with low baseline blood eosinophil count ($< 500/\mu\text{L}$) than in patients with high baseline blood eosinophil counts ($\geq 500/\mu\text{L}$): 11 of 15 patients (73.3%) and 15 of 40 patients (37.5%), respectively ($P = 0.032$; **Table 4**). The baseline serum LDH levels were significantly lower in EASI-75 responders than in EASI-75 non-responders (283.8 ± 85.8 U/L vs. 366.9 ± 116.6 U/L, $P = 0.007$; **Table 3**). The EASI-75 response rate at week 16 was significantly higher in patients with low baseline serum LDH levels (< 400 U/L) than in patients with high baseline serum LDH levels (≥ 400 U/L): 25 of 45 patients (55.6%) and 1 of 10 patients (10.0%), respectively ($P = 0.013$; **Table 4**).

The EASI-75 response rate at week 16 did not differ between patients with baseline serum total IgE $< 3,000$ kU/L (13/25 patients, 52.0%) and those with serum total IgE $\geq 3,000$ kU/L (13/31 patients, 41.9%, $P = 0.453$; **Table 4**). The EASI-75 response rate at week 16 from baseline was not significantly different according to the numbers of sensitized allergen groups (**Table 5**). The serum levels of total and HDM-specific IgE antibodies were significantly reduced from baseline at 52 weeks of monthly dupilumab therapy ($P < 0.001$, **Fig. 3** and **Supplementary Table S1**).

Influence of initial dupilumab dose and concomitant treatments on clinical efficacy

There was no significant difference in the proportion of EASI-75 responders according to the initial dose (300 or 600 mg) of dupilumab at baseline (48.1% vs. 51.9%, $P = 0.431$;

Table 3. Comparison of clinical characteristics and laboratory parameters measured at baseline and week 16 between patients who showed a favorable clinical response (EASI-75 responders) and patients who did not (EASI-75 non-responders) to monthly dupilumab therapy at week 16

Characteristics/laboratory parameters	EASI-75 responders* (n = 27)	EASI-75 non-responders* (n = 30)	P value
Age (yr)	28.4 ± 6.8	31.7 ± 10.0	0.246
Male	18 (66.7)	26 (86.7)	0.114
Onset age of AD (yr)	6.9 ± 9.3	9.0 ± 11.6	0.294
Duration of AD (yr)	21.5 ± 8.5	22.7 ± 9.4	0.683
BMI (kg/m ²)	21.3 ± 2.6	22.7 ± 3.0	0.100
Initial dose of dupilumab			
300 mg	13/27 (48.1)	18/30 (60.0)	0.431
600 mg (loading dose)	14/27 (51.9)	12/30 (40.0)	
EASI score at baseline	27.9 ± 12.5	27.7 ± 10.0	0.854
Baseline serum total IgE (kU/L)	2,881.6 ± 1,868.3	3,336.9 ± 1,825.5	0.278
Blood eosinophil count (/ μ L)			
Baseline	719.2 ± 526.9 (n = 26)	1,251.7 ± 841.2 (n = 29)	0.008
Week 16	421.1 ± 317.2 (n = 19)	988.0 ± 793.9 (n = 25)	0.005
Change from baseline (%)	-18.4 ± 87.3	-13.4 ± 61.7	0.577
Serum LDH (U/L)			
Baseline	283.8 ± 85.8 (n = 26)	366.9 ± 116.6 (n = 29)	0.007
Week 16	216.4 ± 72.6 (n = 19)	236.2 ± 39.9 (n = 25)	0.052
Change from baseline (%)	-24.8 ± 26.9	-33.6 ± 17.4	0.362
Concomitant treatment			
Oral methotrexate	18/27 (66.7)	22/30 (73.3)	0.583
Topical calcineurin inhibitor	10/27 (37.0)	10/30 (33.3)	0.770
Topical corticosteroids	7/27 (25.9)	8/30 (26.7)	0.949
Allergen immunotherapy	4/27 (14.8)	8/30 (26.7)	0.273
Oral corticosteroids	1/27 (3.7)	3/30 (10.0)	0.613
Oral cyclosporine	1/27 (3.7)	3/30 (10.0)	0.613

Data are presented as mean ± standard deviation or n/n_{total} (%). P values of continuous or categorical variables were calculated using the Mann-Whitney U test or χ^2 test (Fisher's exact test was used when more than 20% of cells in the contingency table have expected frequencies less than 5).

EASI, Eczema Area and Severity Index; EASI-75, a decrease of at least 75% in the EASI score from baseline; AD, atopic dermatitis; BMI, body mass index; LDH, lactate dehydrogenase.

*EASI-75 responders/non-responders were determined by the achievement of EASI-75 response at week 16.

Table 4. Comparisons of baseline laboratory parameters between patients who showed a favorable clinical response (EASI-75 responders) to monthly dupilumab therapy at week 16

Laboratory parameters	EASI-75 responder*	P value
Baseline blood eosinophil count		
< 500/ μ L	11/15 (73.3%)	0.032
≥ 500/ μ L	15/40 (37.5%)	
Baseline serum LDH		
< 400 U/L	25/45 (55.6%)	0.013
≥ 400 U/L	1/10 (10.0%)	
Baseline serum total IgE		
< 3,000 kU/L	13/25 (52.0%)	0.453
≥ 3,000 kU/L	13/31 (41.9%)	

Data are presented as n/n_{total} (%). P values were calculated using χ^2 test.

EASI, Eczema Area and Severity Index; EASI-75, a decrease of at least 75% in the EASI score from baseline; LDH, lactate dehydrogenase; IgE, immunoglobulin E.

*EASI-75 responders were determined by the achievement of the EASI-75 response at week 16.

Table 3). During monthly dupilumab therapy, the indicated numbers of the 57 patients were concomitantly treated with the following agents: oral methotrexate, 40 (70.2%); TCI, 20 (35.1%); TCS, 16 (28.1%); and allergen immunotherapy, 12 (21.1%) (**Table 1**). Oral corticosteroids and oral cyclosporine were administered to 4 patients (7.0%). The EASI-75 response rate was not significantly different between patients who were treated with and without oral methotrexate (18/40 patients, 45.0% vs. 9/17 patients, 52.9%; $P = 0.583$), TCI (10/20 patients, 50.0% vs. 17/37 patients, 45.9%; $P = 0.770$), TCS (7/15 patients, 46.7% vs. 20/42 patients, 47.6%; $P = 0.949$), allergen immunotherapy (4/12 patients, 33.3% vs. 23/45 patients, 51.1%; $P = 0.273$), oral corticosteroids (1/27 patients, 3.7% vs. 3/30 patients, 10.0%;

Table 5. Proportions of patients who showed a favorable clinical response (EASI-75 responders) and those without (EASI-75 non-responders) according to the number of sensitized allergen groups

Number of sensitized allergen groups	EASI-75 responder* (n = 27)	EASI-75 non-responder* (n = 30)
0 (n = 2)	2/2 (100%)	0/2 (0%)
1 (n = 18)	7/18 (38.9%)	11/18 (61.1%)
2 (n = 29)	13/29 (44.8%)	16/29 (55.2%)
3 (n = 8)	5/8 (62.5%)	3/8 (37.5%)

Data are presented as n/n_{total} (%).

EASI, Eczema Area and Severity Index; EASI-75, a decrease of at least 75% in EASI score from baseline; IgE, immunoglobulin E.

*EASI-75 responder/non-responder was determined by the achievement of the EASI-75 response at week 16. The number of sensitized allergen groups (house dust mites, molds, and animal dander were regarded as each group) was determined by baseline allergen-specific IgE levels (considered sensitized when the value was higher than 0.35 kU/L).

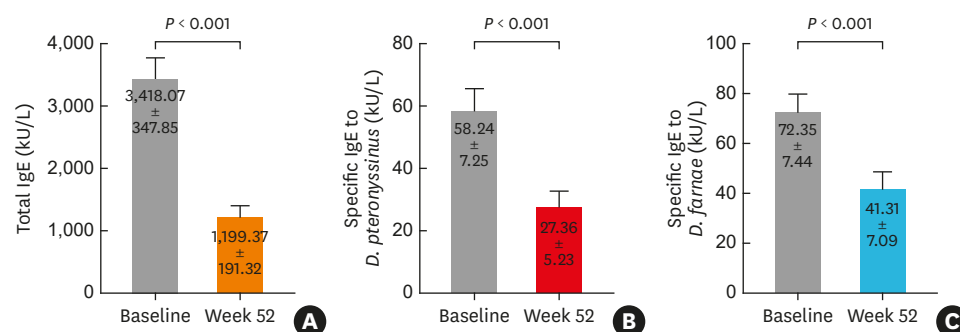


Fig. 3. Changes in serum levels of total IgE (A) and specific IgE to *Dermatophagoides pteronyssinus* (B) and *Dermatophagoides farinae* (C) from baseline at week 52 in 27 patients with AD who received monthly dupilumab therapy.

Data are means ± standard error of the mean. P values were calculated using Wilcoxon-signed rank test. IgE, immunoglobulin E; AD, atopic dermatitis.

P = 0.613), and oral cyclosporine (1/27 patients, 3.7% vs. 3/30 patients, 10.0%; P = 0.613) (Table 3).

Compliance with monthly dupilumab therapy

The total compliance of monthly dupilumab therapy for 16 weeks was 48.7% (57 of 117 patients) in this study. The reasons for discontinuation of dupilumab therapy before week 16 were self-discontinuation due to insufficient clinical response (11 patients), exacerbation of AD (2 patients), and conjunctivitis (1 patient). In addition, 16 patients transferred to national hospitals, where they continued dupilumab therapy at a lower cost. The reason for discontinuation before week 16 could not be evaluated in the remaining 30 patients because of the loss to follow-up or no response to a telephone survey.

Safety

Adverse events were observed in 7 of 57 patients (12.3%) during monthly dupilumab therapy for 16 weeks. Clinical symptoms of conjunctivitis were observed in 4 (7.0%) patients, and 3 (5.3%) experienced AD exacerbation. Conjunctivitis was relieved with antihistamine or corticosteroid eye drops, and none of the patients had a history of conjunctivitis before dupilumab therapy. AD exacerbation was spontaneously resolved in all 3 patients within a month without discontinuing dupilumab therapy or administering rescue medications. Among the 117 patients who received monthly dupilumab therapy more than once at our clinic (including the 57 patients who received monthly dupilumab therapy for 16 weeks), there were a total of 11 patients who experienced adverse reactions: AD exacerbation in 6 patients and conjunctivitis in 5 patients.

DISCUSSION

This study showed that monthly dupilumab therapy was effective and safe in adults with moderate-to-severe AD in real clinical practice. Monthly dupilumab therapy showed EASI-50 and EASI-75 responses in 84.2% and 47.4% of adult patients with moderate-to-severe AD at week 16, respectively. Previous RCTs not allowing concomitant treatments for AD reported EASI-50 and EASI-75 response rates of 65.2%–68.8% and 44.2%–51.3%, respectively, at week 16 in patients treated biweekly with dupilumab.⁸ The EASI-50 (85.7%–98.1%) and EASI-75 (60.6%–81.5%) response rates at week 16 with concomitant medications in the real clinical practice were reported to be higher in recently published real-world studies than in our study.^{11,24–26} In these real-world studies, dupilumab was administered biweekly, which may explain why the clinical outcomes were better in those studies than in our study.

To the best of our knowledge, this study is the first real-world study to report the clinical efficacy of monthly dupilumab therapy in adult patients with moderate-to-severe AD. Dupilumab is currently recommended to be administered to patients with moderate-to-severe AD subcutaneously at a dose of 300 mg every 2 weeks for maintenance therapy.²⁷ In Korea, dupilumab was approved by the Korean Food and Drug Administration in March 2018, and has been prescribed since September 2018. From January 2020, dupilumab treatment cost has been reimbursed by the National Healthcare Insurance of Korea to adult patients with severe AD not adequately controlled by systemic cyclosporine or methotrexate. The National Healthcare Insurance of Korea only covers dupilumab treatment in patients with severe AD whose EASI score \geq 23 even after systemic therapy with immunosuppressants (cyclosporine or methotrexate) for at least 3 months.

In this study, dupilumab was administered to the patients from August 2018 to August 2019, when the National Healthcare Insurance of Korea had not covered dupilumab for the treatment of AD. Patients were required to pay the entire cost of dupilumab during the study period, 808 USD (970,000 KRW) for 300 mg dupilumab. Biweekly dupilumab therapy cost 1,616 USD (1,940,000 KRW) each month, and could be a financial burden for patients with AD in developing countries without support from a national or private healthcare insurance system. Therefore, monthly dupilumab therapy could be a clinically useful, cost-effective, and humanistic treatment option for moderate-to-severe AD patients.

The clinical efficacy of Janus kinase (JAK) inhibitors has been demonstrated in patients with AD in recent RCTs.^{28,29} Methotrexate has been used to treat various inflammatory diseases, including rheumatoid arthritis and AD, and it inhibits the JAK pathways.^{1,30,31} In our study, weekly methotrexate and monthly dupilumab therapies were concomitantly administered to 40 (70.2%) of 57 patients with AD who received monthly dupilumab therapy for 16 weeks. There was no difference in the EASI-75 response rate between patients with and without concomitant methotrexate therapy. Theoretically, combining dupilumab and a JAK inhibitor could inhibit Th2 inflammation at the levels of both cytokine receptor and intracellular signaling pathway, and might provide additive or synergistic clinical effects in patients with AD. Further studies are needed to evaluate the possible clinical usefulness of combination therapy with dupilumab and JAK inhibitor.

In this study, the percentage decrease in the EASI score from baseline at week 16 was significantly inversely correlated with baseline blood eosinophil count and serum LDH level. The EASI-75 response at week 16 was significantly more frequently observed in patients with

low baseline blood eosinophil counts ($< 500/\mu\text{L}$) than in patients with high baseline blood eosinophil counts ($\geq 500/\mu\text{L}$), and in patients with low baseline serum LDH levels ($< 400 \text{ U/L}$) than in patients with high baseline serum LDH levels ($\geq 400 \text{ U/L}$). A previous real-world study presented the positive correlations between baseline serum LDH and baseline EASI score, and between the changes in serum LDH and the EASI score from baseline at 3 months.¹² These findings suggest that the baseline serum LDH level and blood eosinophil count could be predictive markers of clinical response to dupilumab therapy. We considered that our results could be derived from relative under-treatment (a lower cumulative dose) with the monthly dupilumab therapy instead of the conventional biweekly regimen. Nevertheless, our results suggest that physicians could adjust the dose and interval of dupilumab therapy based on baseline systemic inflammation and the patient's economic condition. Further studies should evaluate the clinical usefulness of the laboratory parameters predicting clinical response to dupilumab therapy and personalized adjustments of the dose and interval of dupilumab therapy based on the laboratory parameters and clinical responses.

Interestingly, baseline serum total IgE level at baseline was not different between EASI-75 responders and non-responders in this study. The EASI-75 response rate at week 16 was not significantly different according to the number of sensitized allergen groups (HDM, skin colonizing mold, and animal dander groups). Although the number of patients with non-allergic (intrinsic) AD was relatively small in our study, there was no significant difference in the EASI-75 response rate between patients with allergic (extrinsic) and those with non-allergic AD.

The clinical improvement following short-term dupilumab therapy might have been attributable to the direct inhibition of receptors of the Th2 cytokines (IL-4 and IL-13). However, significant decreases in serum levels of total and allergen-specific IgE were observed at week 52 after monthly dupilumab therapy. These results suggest that a long-term clinical benefit could be sustained even after discontinuing dupilumab therapy in adult patients with AD who showed marked decreases in serum levels of total and allergen-specific IgE. This could be similar to the sustained decreases in serum IgE levels and long-term clinical improvements observed in patients with respiratory allergic diseases during and after completing allergen immunotherapy.³² The possibility of the disease-modifying effect of dupilumab therapy and long-term clinical improvement even after the discontinuation of treatment should be evaluated in future studies.

This study has some limitations. This was a retrospective study with a relatively small number of patients, and we did not include patients as a control group who did not receive dupilumab therapy to compare with the patients treated with monthly dupilumab therapy. We measured a limited number of laboratory parameters for representing systemic and allergic inflammation. Future prospective studies with large patient populations and long-term treatment with dupilumab should be performed to evaluate the clinical efficacy and potential predictive laboratory parameters of monthly dupilumab therapy.

In conclusion, monthly dupilumab therapy was clinically effective in adult patients with moderate-to-severe AD in real clinical practice. Baseline blood eosinophil count and serum LDH level could be predictive markers for clinical response to dupilumab therapy.

SUPPLEMENTARY MATERIAL

Supplementary Table S1

Comparison of serum levels of total IgE and specific IgE to house dust mites measured at baseline and week 52 and percentage changes from baseline at week 52 between patients who received and patient who did not receive allergen immunotherapy

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